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评 述

# 溶血磷脂酰胆碱在肥胖相关代谢性疾病中的研究进展

洪烨, 倪艳, 傅君芬*

浙江大学医学院附属儿童医院内分泌科, 国家儿童健康与疾病临床医学研究中心, 杭州 310052
* 联系人, E-mail: fjf68@zju.edu.cn

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**摘要** 溶血磷脂酰胆碱(lysophosphatidylcholines, LPCs)是人体丰度最高的溶血甘油磷脂, 可直接作用于靶蛋白, 或转换为其他磷脂, 在神经系统和周围代谢器官中发挥重要的生理功能. 临床研究表明, 肥胖、糖尿病、非酒精性脂肪肝病患者血液中多种LPCs浓度下降, 且LPCs浓度与身体测量指标及血液检测指标存在相关性, 可有效鉴别肥胖及其相关代谢性疾病, 预测疾病严重程度, 具有潜在的生物标记物功能. LPCs还具有改善肥胖表型、缓解炎症、抑制脂肪从头合成的作用. 本文将系统整理LPCs的基本代谢和生理功能, 深入探究LPCs在肥胖相关代谢性疾病中的浓度变化和生物学作用, 为肥胖及相关代谢性疾病的诊疗提供新思路.

**关键词** 溶血磷脂酰胆碱, 脂质代谢, 肥胖, 肥胖相关代谢性疾病

肥胖及相关代谢性疾病, 如非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)、代谢综合征、2型糖尿病(Type 2 Diabetes, T2D)等, 严重威胁儿童和成人健康, 已成为我国重大的公共卫生问题[1,2]. 脂质代谢异常是肥胖及其相关代谢性疾病的重要特征, 其中溶血磷脂酰胆碱(lysophosphatidylcholines, LPCs)浓度异常多有报道, 与肥胖等代谢性疾病的发生密切相关[3~6]. LPCs作为人体丰度最高的溶血甘油磷脂, 可与磷脂酰胆碱(phosphatidylcholines, PCs)相互转化, 是人体组织细胞磷脂重塑的核心[7,8]. 全面认识LPCs基本代谢, 及其在肥胖相关代谢性疾病中的生物学作用, 有助于理解疾病病理过程, 探寻新的诊疗方法.

## 1 LPCs基本介绍

LPCs在结构上以甘油基团为骨架, 1位碳有脂肪酸链, 3位碳有磷酸基团和胆碱基团. 按照脂肪酸链特性, 如碳原子数量、碳链饱和程度可将LPCs进一步细分, 如LPC12:0, LPC14:0, LPC16:0, LPC18:0, LPC18:2, LPC18:4等[9]. LPCs分布在细胞内和细胞外, 胞内LPCs浓度较低, 一般作为细胞代谢物; 胞外LPCs浓度较高, 健康成年人血浆总LPCs水平为150~300 μmol/L, 其中LPC16:0含量最高, 其次是LPC18:0, LPC18:2和LPC18:1[10]. 一般情况下, 血浆中LPCs与白蛋白直接结合, 且LPC-白蛋白复合物的解离常数($K_d$)为25 μmol/L[11];

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在炎症发生时，LPCs与白蛋白的结合能力受损，取而代之的是LPCs与酸性糖蛋白(acidglycoprotein，AGP)结合[12].

### 1.1　LPCs的来源

LPCs可由PCs转换而来. 分泌型磷脂酶$A_2$(secreted phospholipase $A_2$, $sPLA_2$)是磷脂酶$A_2$(phospholipase of type $A_2$, $PLA_2$)超家族重要一员，包含11个亚型[13]. 其中，$sPLA_2$-1B经胰腺腺泡细胞分泌入肠道，在胆汁酸的辅助下，水解食物中的PC sn-2位酯键，生成LPCs和脂肪酸[9,13]. $sPLA_2$-2A在血浆中含量丰富，其水平在某些疾病状态中上升[13]，除直接水解血浆中的PCs，$sPLA_2$-2A还可将细胞外囊泡的磷脂成分催化水解为LPCs[14]. 胞浆型磷脂酶A2(cytosolic phospholipase $A_2$, $cPLA_2$)是$PLA_2$超家族的另一大类，共有6个亚型，其中$cPLA_2\alpha$是研究较多的一类，几乎所有组织均有表达，在胞内钙离子刺激下，$cPLA_2\alpha$由胞浆向核周膜，比如内质网膜、高尔基体膜转运，并进一步水解这些生物膜中的PCs成分[15,16](图1). 另外，血浆中的卵磷脂胆固醇脂酰转移酶(lecithin-cholesterol acyltransferase, LCAT)也可将PCs sn-2位上的脂肪酸转位给胆固醇，生成LPCs和胆固醇酯[17]. 血管内皮细胞表面的内皮酯酶(endothelial lipase, EL)可以水解高密度脂蛋白中的PCs成分，释放脂肪酸和LPCs[18].

除经PCs转换而来，LPCs还可由肝细胞分泌(图1). 肝细胞可以直接合成、释放LPCs，并在细胞外与白蛋白结合，此外白蛋白促进LPCs的释放[19]. LPCs还可以作为脂蛋白(如低密度脂蛋白LDL，高密度脂蛋白HDL)的成分被分泌至血液，并且LPCs可自发性地从LDL转移至HDL中[20,21].

### 1.2　LPCs的去路及效应分子

LPCs可以被转化为其他代谢物. 在溶血磷脂酰胆碱酰基转移酶(lysophosphatidylcholine acyltransferases, LPCATs)的作用下，LPCs接收一份子脂肪酸，重新转换为磷脂酰胆碱PCs，该通路与$PLA_2$的催化过程合称为Lands循环[7](图1). 与$PLA_2$类似，LPCATs也有多种亚型，包括LPCAT 1-4，且每种亚型有其组织分布和特点，其中LPCAT3亚细胞定位于内质网，广泛表达在肝脏、小肠、肌肉等代谢相关组织[7,22]，最近的研究揭示LPCAT3的电镜结构，发现其以特定结构域与LPCs相结合[23]. Autotaxin(ATX)又称自分泌运动因子，是一种分泌型糖蛋白，能将LPCs通过脱胆碱基转化为溶血磷脂酸(lysophosphatidic acids, LPAs). ATX有5种亚型，分别是α, β, γ, δ, ε, 其中ATX-β广泛分布于外周组织和血浆[24]. 水解产生的LPA可与细胞膜上的G蛋白偶联受体(G-protein-coupled receptors, GPCRs)，溶血磷脂酸受体(LPAR)1-6作用，激活下游信号分子，发挥多种生理和病理功能[25,26](图1). 在肥胖相关代谢性疾病中，探索LPCATs, ATX在不同组织中的表达情况有助于进一步理解LPCs水平变化的原因.

LPCs的靶分子一直是科学家关注的问题. 早在2000年，有科学家报道G蛋白偶联受体G2A可以作为LPCs的受体[27]，虽然LPCs与G2A直接结合的证据不足，但后续的研究通过不同方式，比如siRNA敲降G2A表达[28]，G2A敲除小鼠模型[29]，G2A中和抗体[30]，G2A受体激动剂等[31]，均证明LPCs与G2A受体功能上存在密切联系. 与LPCs有功能联系的G蛋白偶联受体还有GPR119[32,33]，最新研究表明，四种LPCs(16:1，18:0，18:1，20:0)作为配体，与受体跨膜域形成的口袋样结构结合，从而被GPR119识别，且这种结合模式与治疗T2D的临床候选药物APD668十分相似，其中LPC18:1与GPR119的结合度最高[34,35]. 其他与LPCs有功能联系的GPCR有：GPR55，GPR40[32,36]，GPR535，GPR120[37]，GPR82[38]. LPCs还可以激活过氧化物酶体增殖受体(peroxisome proliferator activated receptors, PPARs)[39~41]，其中作为PPARr的配体，LPCs(16:0, 18:0, 18:1)结合在由不同结构域形成的配体结合区[40,42]. 另外，LPCs可激活Toll样受体(Toll-like receptor, TLR)发挥下游功能[43](图1).

### 1.3　LPCs的生理功能

分泌型磷脂酶A2($sPLA_2$)可以水解肠腔中的PCs生成LPCs，后者在远端肠道被肠上皮细胞摄入后，参与乳糜微粒的形成，促进脂质的吸收[44,45]. LPCs可作为生物膜的组成成分，因其只带有一条脂肪酸链，能够降低膜的致密性，增加膜的流动性[46]. LPCs还可作为脂肪酸的运载体. DHA(docosahexaenoic acid)，即二十二碳六烯酸，在脑中的丰度很高，对脑发育和认知功能至关重要. 位于血脑屏障内皮细胞表面的主要促进因子超家族成员2a(major facilitator superfamily domain containing 2a，Mfsd2a)可以将DHA以LPCs的形

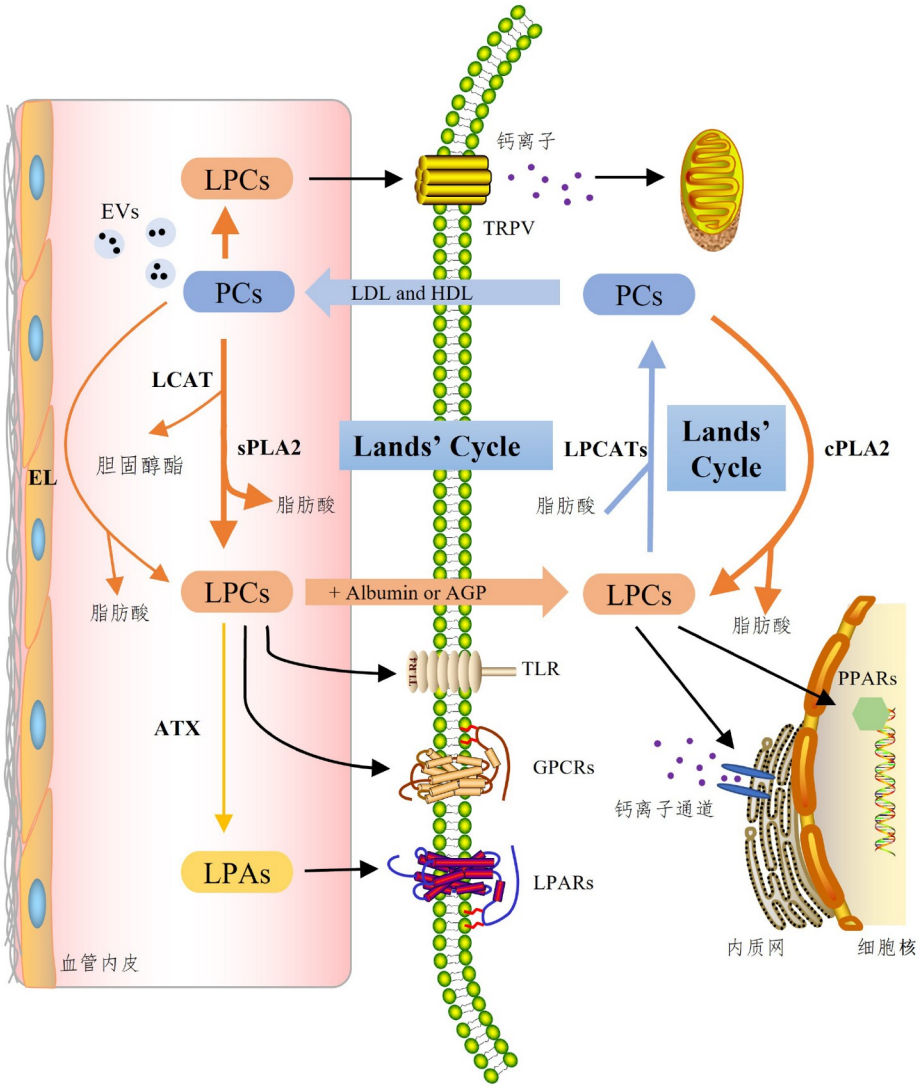


**图 1** LPCs的基本代谢与下游效应分子. 在LPCATs作用下, 胞浆中的LPCs转换为PCs; PCs在cPLA2催化下转变为LPCs, 循环中的PCs(包括含有PCs的脂蛋白、EVs)在sPLA2作用下转换为LPCs. LPCs与PCs之间的转换称为Lands循环. LCAT以及EL可将PCs水解形成LPCs. LPCs可被ATX转换成LPAs, 后者借助其受体LPAR1-6发挥下游功能. LPCs可通过细胞膜表面的GPCRs发挥效应. LPCs可作用于离子通道调节胞内钙离子浓度, 比如钙离子通道和TRPV离子通道. LPCs还可通过PPARs调控细胞信号通路. PPARs: 过氧化物酶体增殖物激活受体; LPARs: 溶血磷脂酸受体

**Figure 1** Basic metabolism of LPCs and downstream target molecules. LPCATs reacylate LPCs into PCs in the cytoplasm, and cPLA2 deacylates PCs into LPCs. sPLA2 generates LPCs by deacylating PCs in circulation (including lipoproteins and EVs that contain PCs). The transition between LPCs and PCs is known as the Lands cycle. LCAT and EL can hydrolyze PCs to generate LPCs. LPCs can be metabolized into LPAs, which exert their effects via six receptors, LPAR1–LPAR6. LPCs exert their effects via GPCRs on the cell membrane. LPCs also regulate $Ca^{2+}$ concentration by targeting ion channels; for example, calcium channels and TRPV ion channels. LPCs can mediate the cell signaling pathway by activating PPARs. PPARs: peroxisome proliferator-activated receptors. LPARs: LPA receptors

式转运进入脑组织[47]. LPC-DHA也可经Mfsd2a转运至眼部, 对于感光细胞的发育十分关键[48]. Mfsd2a在肝脏门静脉周围的肝细胞有少量表达, 但特定条件会刺激Mfsd2a表达上调, 对肝细胞摄入LPCs、肝细胞脂滴生成、肝细胞再生发挥重要调控作用[49,50]. 禁食条件下肝脏来源的LPCs释放入血, 进入大脑后LPCs可被星形胶质细胞表面的ATX水解为LPAs, 后者具有增加大脑皮层兴奋性和促进摄食行为的功能[51]. LPCs还可影响离子通道, 调控细胞内的离子浓度, 比如具有第二信使作用的$Ca^{2+}$[52,53]; 在痛觉发生过程中, LPC16:0可通

过作用于酸传感离子通道3参与调节痛觉[54]，而LPC18:0通过作用于瞬时受体电位香草酸家族(transient receptor potential vanilloid, TRPV)1型和2型受体参与调节痛觉[55]. LPCs的靶分子中, GPR119主要表达在胰岛β细胞和胃肠道的内分泌细胞, LPCs结合GPR119参与调节胰岛素分泌和糖代谢[56]. 以上证据表明, LPCs生理功能广泛, 涵盖周围代谢组织和中枢神经系统(图2).

## 2　LPCs在肥胖相关代谢性疾病中的浓度变化

### 2.1　临床研究

有较多研究关注肥胖及其相关代谢性疾病发生时LPCs的浓度变化. 肥胖成人血浆中大多数LPCs水平较对照组显著下降, 且这种差距在减重后依旧存在[57]. 针对高加索女性的代谢组学分析发现, 肥胖患者血清中LPCs水平下降[4]. 孕期肥胖母亲血浆中的LPC18:0显著降低[58]. 利用高胰岛素钳夹实验把纳入的人群(BMI>25 kg/m$^2$)分为胰岛素敏感组和胰岛素抵抗组, 脂质组学检测发现胰岛素抵抗组的血浆LPCs水平更低[59]. 一项针对中国人群的研究发现, 超重/肥胖组血清中不饱和LPCs水平(LPC18:1和LPC18:2)显著下降[60]. 考虑到代谢性疾病伴随着免疫状态的改变, Wilkin等人[61]分析外周血单个核细胞(peripheral blood mononuclear cell, PBMC)的脂质组成分变化, 发现大多数LPCs在肥胖伴有血糖紊乱患者PBMC中明显下降, 其中LPC20:0和LPC20:3水平下降明显, 作者提出这两种LPCs可以作为区分两种肥胖类型的标志物. 另外, 肥胖个体肌肉组织中LPC16:1, LPC16:0较对照组明显下降[46]. 也有研究报道LPC18:1下降, LPC14:0, LPC18:0增加[62].

糖耐量受损是糖尿病前期的重要表现, 糖耐量受损人群血清中LPC18:2较糖耐量正常人群显著降低[63]; 其他下降的LPCs包括: LPC16:0, LPC17:0, LPC18:0, LPC18:1, LPC18:2, LPC18:3, LPC20:3, LPC20:4,

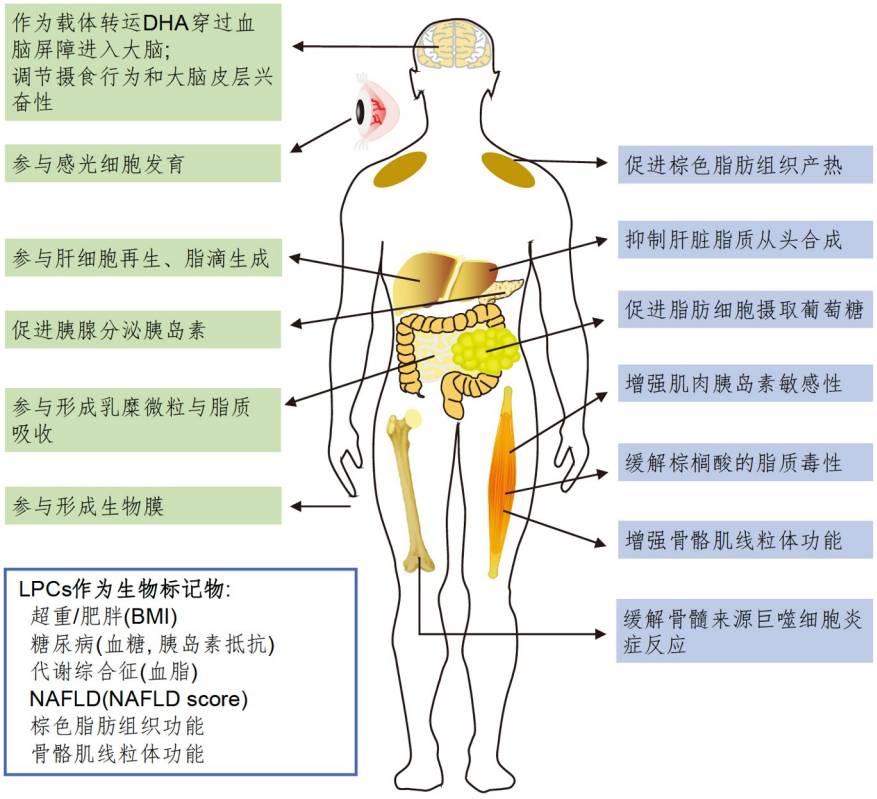


**图 2**　LPCs的生理功能(绿框)以及在肥胖相关代谢性疾病中的作用(蓝框)

**Figure 2**　Physiological functions (green boxes) and roles of lysophosphatidylcholines (blue boxes) in obesity-related metabolic diseases

LPC20:5, LPC22:5, LPC22:6[64]. 对于已诊断的T2D患者, 血清或血浆中也有多种LPCs水平显著降低[63~65]; 而在所有纳入的肥胖患者中, 伴有糖尿病的个体血浆中LPCs进一步降低[66,67]. 除循环中的LPCs, Diamanti等人[68]还发现T2D患者肌肉中LPC16:0, LPC16:1, LPC18:0, LPC18:1, LPC18:2, LPC18:3等显著降低.

在NAFLD的早期阶段, 血清中LPC24:1显著下降[69]. 相比于对照组, 非酒精性脂肪肝(non-alcoholic fatty liver, NAFL)和非酒精性脂肪肝炎(non-alcoholic steatohepatitis, NASH)患者血清中的总LPCs有下降趋势[70], 另有研究则发现NAFLD患者血清中总LPCs显著降低, 其中LPC15:0, LPC17:0, LPC18:1下降最为明显[71]. 虽然LPCs在NAFLD中的变化也有不一致的结果, 比如NAFL组LPC20:4和LPC20:5没有改变, LPC22:6增加[72], 更多证据表明大多数且丰度较高的LPCs分子, 如LPC16:0, LPC18:0, LPC18:2, LPC18:3, LPC20:3, LPC20:4在NAFLD患者血清中显著降低[72~76]. 值得注意的是, 相对于NAFL-胰岛素抵抗的患者, NAFL-胰岛素敏感患者血浆中LPC16:0更高, 且高水平的LPC16:0与胰岛素敏感性呈正相关[77]. 随着研究深入, 代谢功能障碍相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD)的概念被提出[78], Babu等人[79]发现在代谢功能障碍相关脂肪肝炎(metabolic dysfunction-associated steatohepatitis, MASH)的患者血清中LPC18:1, LPC18:3, LPC20:3下降. 代谢综合征也是肥胖的常见并发症, 包括糖、脂代谢异常、高血压, 肥胖伴代谢综合征的患者血清中总LPCs水平显著下降[80].

健康儿童血浆中总LPCs含量为(155.74±19.72) μmol/L[3], 与健康成人接近. 我国肥胖儿童血浆中的LPCs水平明显降低[81]; 一项北京大学的研究报道, 无论血脂是否有异常, 肥胖男孩血浆中的五种LPCs比对照组明显降低, 分别是LPC18:1, LPC18:2, LPC20:0, LPC20:1, LPC20:2[3]. 国外研究也发现, 肥胖儿童血浆中多数LPCs水平下降[82~84], 包括LPC14:1, LPC18:1, LPC18:2和LPC20:4, 其中LPC18:2几乎下降了一半, 从36.37 μmol/L下降到18.09 μmol/L[83]. 在另一项以肥胖儿童为对象的研究中, 有肝脏脂肪变性的患者血清中LPCs与没有脂肪变性的患者血清中LPCs水平接近[85], 提示肝脏的进一步病变不会加剧LPCs水平减少. 对于肥胖儿童进行锻炼, 营养教育等干预后, 部分儿童体重降低, 检测这些儿童体重恢复后血清代谢物的水平, LPC18:1, LPC18:2和LPC20:4显著增加[86].

### 2.2 动物研究

肥胖小鼠模型可由基因缺陷或者饮食干预获得. 高脂喂养柏林肥胖小鼠可诱导明显的肥胖表型和胰岛素抵抗, 质谱检测发现造模组小鼠血清中LPC16:1和LPC18:1下降显著[87], 这两个LPCs分子在单纯高脂饮食诱导的FVB/N肥胖小鼠血清中也下降[88]; 此外, C57BL/6肥胖小鼠血清中LPC16:1, LPC18:2, LPC18:3, LPC20:0相较于对照组下降[89], 这些结果提示LPCs下降在不同品系的肥胖小鼠中具有普遍性. 其他含有长链脂肪酸且水平下降的LPCs包括: LPC20:0, LPC20:1, LPC20:3, LPC20:4[90]. 一项研究同时探究肥胖小鼠血清和肝脏组织的LPCs水平, 发现血清中大多数LPCs下降; 肝脏中LPC14:0, LPC16:0, LPC16:1, LPC18:0, LPC18:3降低[91]. 然而, 部分研究也发现LPC17:0, LPC18:1, LPC18:3, LPC20:0, LPC20:3, LPC22:1, LPC22:4等在肥胖小鼠血清中增加[92,93], 表明肥胖小鼠实验结果存在不一致. 肥胖组小鼠皮下白色脂肪组织中多种LPCs也下降[94](表1).

在用蛋氨酸、胆碱缺乏饮食诱导的NASH小鼠血清中, LPC16:0, LPC18:0, LPC18:1显著下降[95]. 类似的, 在胆碱缺乏性左旋氨酸饮食构建的NAFLD小鼠模型中, 血清中LPC18:1, LPC18:0, LPC20:0, LPC22:0, LPC22:1, LPC22:6, LPC24:0均有明显下降[96]. 给高脂高糖喂养的猪模型出现体重增加, 糖耐量异常, 肝脏炎细胞浸润, 其血浆中大多数LPCs水平下降[97]. 四氯化碳处理肥胖小鼠可以造成明显的NASH表型, 包括肝细胞气球样变, 炎症以及纤维化, 在这种NASH模型中, 肝脏组织的LPC18:1和LPC20:4明显上升[98], 提示LPCs水平变化与动物造模方式有关.

### 2.3 LPCs浓度变化的调节因子

LPCATs和ATX是LPCs代谢通路上的两个关键酶, 是影响LPCs浓度的重要因子. 作为一种胞浆蛋白, LPCATs可以将LPCs转化为PCs, 其表达增加将显著影响LPCs的含量, 改变PC/LPC的比值. 与对照组相比, 肥胖人群肌肉活检组织中LPCAT3表达增加, LPCs水平下降, 溶血磷脂与磷脂的比值下降, 这在肥胖小鼠的肌肉组织中得到验证[46]. 另有研究报道, 无论是高脂

**表 1**　LPCs在血液和组织样本中的水平变化

**Table 1**　Changes of LPCs level in circulating and tissues

| 疾病类型 | 样本类型 | LPC变化 | 发表年份 |
|---|---|---|---|
| 成年人 | | | |
| 肥胖 | 血浆 | 肥胖组LPC15:0, LPC18:3, LPC18:2, LC18:1, LPC20:5, LPC20:4, LPC20:0, LPC22:6, LPC22:5下降 | 2014[57] |
| 肥胖 | 血清 | 肥胖组LPC14:0, LPC 15:0, LPC16:0, LPC16:1, LPC17:0, LPC18:0, LPC18:1, LPC18:2, LPC20:0, LPC20:1, LPC20:4下降 | 2023[4] |
| 肥胖 | 血浆 | 肥胖组LPC18:0显著下降 | 2019[58] |
| 肥胖(伴或不伴胰岛素抵抗) | 血浆 | 肥胖伴胰岛素抵抗组LPC20:0, LPC20:1, LPC22:1下降 | 2016[59] |
| 肥胖/超重 | 血清 | 不饱和LPCs显著下降(LPC18:1和LPC18:2) | 2018[60] |
| 肥胖(伴或不伴血糖异常) | PBMC | 肥胖伴血糖异常组大多数LPCs水平下降, 其中LPC20:0和LPC20:3 下降显著 | 2021[61] |
| 肥胖 | 肌肉 | 肥胖组LPC16:1, LPC16:0显著下降 | 2021[46] |
| 肥胖/超重 | 血浆 | 超重/肥胖组LPC18:1显著下降, LPC20:2, LPC18:2 没有显著差异, LPC14:0, LPC18:0上升 | 2010[62] |
| T2D和糖耐量受损 | 血清 | 糖耐量受损组和糖尿病组LPC18:2显著下降 | 2012[63] |
| T2D和糖耐量受损 | 血浆 | 糖耐量受损组和糖尿病组LPC17:0, LPC18:0, LPC18:1, LPC18:2, LPC18:3, LPC20:3, LPC20:4, LPC20:5, LPC22:5, LPC22:6下降 | 2016[64] |
| T2D | 血清 | 糖尿病组LPC18:2显著下降 | 2013[65] |
| T2D | 血浆 | 糖尿病组总LPCs以及LPC16:0, LPC18:0, LPC19:0, LPC18:1, LPC20:0, LPC20:1, LPC20:2均下降 | 2020[66] |
| T2D | 血浆 | 糖尿病组LPC18:0, LPC18:1, LPC18:2下降 | 2020[67] |
| T2D | 血浆<br>肌肉 | 糖尿病组LPC16:0, LPC16:1, LPC18:0, LPC18:1, LPC18:2, LPC18:3 下降 | 2019[68] |
| NAFLD | 血清 | NAFLD组LPC24:1显著下降 | 2022[69] |
| NAFLD | 血清 | NAFLD组总LPCs有下降趋势 | 2018[70] |
| NAFLD | 血清 | NAFLD组LPC15:0, LPC17:0, LPC18:1显著下降 | 2021[71] |
| NAFLD | 血浆 | NAFLD组LPC18:2显著下降, LPC20:4和LPC20:5没有改变, LPC22:6在NAFL组增加 | 2016[72] |
| NAFLD | 血清 | NAFLD组LPC16:0显著下降 | 2019[73] |
| NAFLD | 血清 | NAFLD组LPC16:0, LPC18:0显著下降 | 2013[74] |
| NAFLD | 血浆 | NASH组LPC16:0, LPC18:0, LPC18:1, LPC18:2, LPC18:3, LPC20:3, LPC20:4显著下降 | 2016[75] |
| NAFLD | 血清 | NAFLD组LPC17:0显著下降 | 2017[76] |
| NAFLD | 血浆 | 相较于胰岛素抵抗组, 血浆中LPC16:0在胰岛素敏感组更高 | 2013[77] |
| MASH | 血清 | MASH组LPC18:2, LPC18:3, LPC20:3显著下降 | 2024[79] |
| 代谢综合征 | 血清 | 患者血清中总LPCs水平较健康组明显降低 | 2022[80] |
| 儿童和青少年 | | | |
| 肥胖 | 血浆 | 肥胖组LPC18:1, LPC18:2, LPC20:2, LPC20:1, LPC20:0下降 | 2019[3] |
| 肥胖 | 血浆 | 肥胖组总LPCs下降 | 2021[81] |
| 肥胖 | 血浆 | 大多数LPCs水平下降 | 2015[82] |
| 肥胖 | 血清 | 肥胖组LPC18:1, LPC18:2和LPC20:4下降 | 2012[83] |
| 肥胖/超重 | 血清 | 肥胖/超重组LPC14:1下降 | 2019[84] |
| 肥胖(伴或不伴肝脏脂肪变性) | 血清 | 肥胖伴有肝脏脂肪变性组LPCs水平与对照组相近 | 2020[85] |
| 动物模型 | | | |
| 肥胖小鼠 | 血清 | 肥胖组LPC16:1, LPC18:1下降 | 2014[87] |

(表1续1)

| 疾病类型 | 样本类型 | LPC变化 | 发表年份 |
|---|---|---|---|
| 肥胖小鼠 | 血清 | 肥胖组LPC16:1, LPC18:1下降, 而LPC18:0, LPC18:2, LPC20:0升高 | 2014[88] |
| 肥胖小鼠 | 血清 | 肥胖组LPC16:1, LPC18:2, LPC18:3, LPC20:0下降, LPC20:3, LPC20:4和LPC22:4升高 | 2014[89] |
| 肥胖小鼠 | 血清 | 肥胖组LPC20:0, LPC20:1, LPC20:3, LPC20:4下降 | 2021[90] |
| 肥胖小鼠 | 血清和肝脏 | 肥胖组血清中LPC14:0, LPC15:0, LPC16:0, LPC16:1, LPC17:1, LPC18:1, LPC18:2, LPC19:0, LPC20:1, LPC20:4下降, LPC17:0, LPC18:0, LPC18:3增加; 肥胖组肝脏中LPC14:0, LPC16:0, LPC16:1, LPC18:0, LPC18:3降低, LPC20:4, LPC22:6增加 | 2011[91] |
| 肥胖小鼠 | 血清 | 肥胖组LPC16:1, LPC18:1, LPC20:0, LPC20:3增加 | 2021[92] |
| 肥胖小鼠 | 血清 | 肥胖组LPC18:1, LPC22:4, LPC22:1增加 | 2022[93] |
| 肥胖小鼠 | 皮下脂肪 | 肥胖组LPC18:2, LPC19:0, LPC20:0, LPC22:0, LPC24:0下降 | 2021[94] |
| NASH小鼠 | 血清 | NASH组LPC16:0, LPC18:0, LPC18:1显著下降 | 2012[95] |
| NAFLD小鼠 | 血清 | NAFLD组多种LPCs显著下降 | 2023[96] |
| NAFLD猪 | 血浆 | NAFLD组多种LPCs显著下降 | 2022[97] |
| NASH小鼠 | 肝脏 | NASH组LPC18:1和LPC20:4明显上升 | 2021[98] |

饲料诱导的肥胖小鼠, 还是基因敲除的肥胖小鼠(ob/ob和db/db)模型, 皮下脂肪组织中LPCAT3表达显著上调, 导致PC/LPC比值增加[99]. 肝脏也是LPCATs表达丰度较高的组织, 在蛋氨酸胆碱缺乏饲料诱导的NASH小鼠模型中, 肝脏LPCAT1-4的表达水平显著上升,导致血清中多种LPCs水平下降[95]. ATX是一种分泌型蛋白, 对于细胞外和循环中的LPCs水平影响更直接. 在肥胖、NAFLD患者, 以及相关动物模型的循环和组织(比如脂肪, 肝脏)中ATX的表达水平均升高, 从而消耗LPCs, 使其下游代谢产物LPAs增加[26,100]. PCs经LCAT的转酰基作用生成LPCs. 在肥胖、代谢综合征等疾病发生时, 血浆或血清中LCAT的活性显著下调[80,101], Bril等人[102]发现NAFLD且伴有重度肝脏纤维化患者血清中LCAT蛋白含量降低, 这些均可导致胆固醇酯化过程受损和代谢产物LPCs水平下降. LPCs的转运体Mfsd2a也能调控LPCs的水平. Mfsd2a在汇管区肝细胞表达量低, 具有节律性. 高脂高糖饮食增加其表达水平, 有助于肝细胞摄取LPCs, 降低循环中LPCs水平. 当特异性敲除肝细胞Mfsd2a后, LPCs不能被肝细胞摄取, 导致血清中LPCs浓度上升[50].

LPCs水平可受到药物干预的影响. 桑枝总生物碱是一种中药提取成分, 已被证明对糖尿病、肥胖和NAFLD具有治疗作用[103,104]. 研究发现, 桑枝总生物碱通过提高LPCs水平缓解肥胖相关表型[105]. LPCs水平还受温度、饮食等因素调节[106,107].

## 3 LPCs在肥胖相关代谢性疾病中的作用

### 3.1 LPCs作为生物标记物

Yin等人[108]最新研究发现成人血浆中17个不同碳链或饱和度的LPCs分子与肥胖发生呈显著负相关, 且四种LPCs(LPC16:0, LPC16:0e, LPC18:0, LPC22:5)与体重指数BMI存在负相关性, Bagheri[109]的研究报道了类似的结果. LPCs水平还与肥胖相关代谢指标呈显著负相关, 国外成年人群血液中多种LPCs(如LPC17:0, LPC18:1, LPC18:2)的水平随着BMI的增加而降低, 两者呈显著负相关[5,110], 中国成人数据也发现LPCs与BMI、总甘油三酯、总胆固醇、收缩压等呈负相关[60]. 儿童人群中LPC14:0, LPC16:1, LPC18:1和LPC18:2与BMI z score呈强负相关[111]. 不仅如此, 在Rzehak等人[112]研究中, 来自六月龄婴儿血浆的LPC14:0是唯一与体重增长呈显著正相关的代谢物, 且对于6岁儿童体重具有预测价值. 对肥胖患者给予低热量饮食后, LPCs分子也表现出很好的预测功能, 其中LPC22:4和LPC22:5可以很好地预测干预后体重下降程度[113]. 因此有学者提出LPCs是可靠的超重/肥胖的生物标记物[114].

LPCs水平不仅与T2D发生(以空腹血糖≥7.0 mmol/L 或者OGTT试验2 h 血糖≥11.1 mmol/L为标准)呈负相关[115,116], 与糖代谢其他指标也有相关性. 临床研究表明, LPC22:5和LPC16:0与胰岛素抵抗(分

别以HOMA-IR和口服糖耐量实验结果为参照)呈显著负相关[64,77]; LPC17:0, LPC18:1, LPC18:2, LPC19:0, LPC20:0, LPC20:1等多种分子水平与HOMA-IR和$HbA_{1c}$均呈负相关[66,117]. 肥胖患者血浆中总LPCs水平, LPC18:1, LPC18:2的水平与肌肉组织的胰岛素敏感指数相关, LPCs水平越高, 肌肉对外周血葡萄糖利用度越高[118]. 动物研究表明, 大鼠生命早期的LPC18:2水平越低, 成年期血糖越高, 两者呈显著负相关, 作者从而提出幼年期血清LPC18:2是成年期血糖水平的预测性标记物[119].

LPCs可有效鉴别代谢综合征. 血清中LPC18:2越低, 甘油三酯水平越高, 两者呈显著负相关[120]. 从德国的人群研究中Sattler等观察到LPC18:2与代谢综合征常见的五种代谢异常(包括腹型肥胖、高甘油三酯、高血压、高空腹血糖、低HDL-胆固醇)均呈现负相关[121]. 血清LPC14:0和LPC15:0水平与高甘油三酯、高血压、高空腹血糖呈强相关性, 并与其他三个代谢物一起构成代谢风险评分[122]. 肥胖也是非酒精性脂肪肝病的危险因子[1], 一项基于儿童群体的研究发现, LPC16:0, LPC18:0与NAFLD的活动评分呈正相关, 其水平变化反映肝脏病变的严重程度[123].

棕色脂肪组织在缓解肥胖相关代谢紊乱中发挥重要功能, 随着棕色脂肪组织体积增多, LPC16:1和LPC16:0水平增加, 呈显著相关; 在用独立队列进行分析时, LPC16:0与棕色脂肪组织活动仍保持正相关, 因此LPC16:0可以作为棕色脂肪组织激活的标记物[124]. 最新研究发现在肾上腺素能刺激下, 棕色脂肪组织产热功能增强, 同时伴有多种分子水平上调, 其中LPC20:4作为脂质生物标记物, 为增强棕色脂肪组织功能提供新靶点[125]. 此外, 血浆中LPC16:1的基线水平越高, 骨骼肌线粒体功能越好; 并且LPC16:1和LPC18:1水平下降越缓, 骨骼肌线粒体功能衰减越慢, 因此Tian等人[126]认为补充LPCs水平可以改善线粒体功能, 并提出进行临床研究的必要性.

### 3.2　LPCs作为干预靶点

LPCs在治疗某些疾病方面, 已表现出良好的干预效果. 通过饮食摄入LPC-DHA, LPC-EPA(eicosapentaenoic Acid, 二十碳五烯酸), 可以有效增加脑部DHA, EPA的浓度[127], 从而改善神经退行性病变、视网膜病、抑郁[128~132]. 越来越多的研究证实LPCs具有改善肥胖相关代谢的作用.

肥胖条件下, 人源肌细胞中LPCs水平降低, 如LPC16:0, LPC16:1; 小鼠肌肉组织特异性敲除LPCAT3, 使得肌肉组织内的LPCs水平增加, 最终效应是增强肌肉组织的胰岛素敏感性[46]. 而在LPCAT3过表达的肌肉组织中, LPCs水平显著下降, 导致力量产生能力较对照组下降, 且这种缺陷在给小鼠喂养高脂饲料时更为严重[133]. 在饮食诱导和db/db小鼠肥胖模型中, 口服LPC18:0改善多种代谢表型, 比如高血糖、高血脂以及肝脏损伤[39,134], 研究进一步发现, LPC18:0作为PPARr激动剂, 促进棕色脂肪组织的产热功能, 表现出和降糖药物罗格列酮类似的效果[39]. 口服LPC17:0也被证明改善肥胖小鼠的胰岛素抵抗[37]. LPC16:0, LPC14:0, LPC12:0可以增强脂肪细胞摄取葡萄糖, 改善糖尿病小鼠的血糖[135]. 肝脏汇管区肝细胞少量表达LPC转运体Mfsd2a, 但是NAFLD条件下表达增多, 摄取血液中的LPCs, 用于肝细胞的脂滴生成, 从而发挥保护作用, 其机制之一在于LPCs(LPC18:1, LPC18:2, LPC22:6)可抑制脂质的从头合成通路[50]. 以上证据表明, LPCs在肌肉、脂肪和肝脏等器官均有改善代谢的作用.

慢性炎症是肥胖相关代谢性疾病的主要特征之一, 棕榈酸在肥胖、NAFLD等代谢性疾病发生时显著升高, 产生脂质毒性, 引起组织炎症[136]. 过多的棕榈酸促进肌细胞表达炎症因子IL6, CXCL3, 而LPC16:0, LPC18:1不仅可以缓解这种脂质毒性, 还可增强胰岛素敏感性, 缓解内质网应激[41]. LPCs可以直接作用于巨噬细胞, 调节免疫反应. LPCs通过上调PPARr表达, 促进巨噬细胞M2型极化相关基因表达, 比如Arginase 1, IL10等. 含有多不饱和脂肪酸链的LPCs有明显抑制炎症的作用[137], 脂多糖诱导Raw 264.7细胞高表达多种炎症因子, 而DHA-LPC可以有效减弱炎症反应, 这与动物实验结果一致[138]. LPCs还可激活下游信号分子TLR, 但与以往研究不同, 其效应是抑制巨噬细胞内NF-kB磷酸化[139]. LPCs抑制TLR通路相关炎症因子在鱼类实验中也得到验证[140].

值得关注的是, LPCs对脓毒症相关炎症有显著缓解作用. 给脓毒症小鼠模型腹腔注射LPC18:0, 循环中HMGB1水平降低; 在体外用LPC18:0处理巨噬细胞和单核细胞, 上清液中HMGB1水平降低, 并且这种抑炎作用依赖于G2A受体[30,141]. 在另一个脓毒症小鼠模型

中, 给小鼠皮下注射LPC18:0, 腹腔灌洗液炎症因子水平显著下降, 肺组织免疫细胞浸润减少, 小鼠存活率上升[142]; 体外实验进一步发现, LPC18:0可以显著降低白细胞IL-1β的表达[143]. 静脉注射LPCs可以减少小鼠器官损伤, 降低循环中IL-1β的水平[144]. 这些动物实验表明, 尽管给药方式不同, LPCs缓解炎症作用明显.

## 4 结论

溶血磷脂酰胆碱LPCs作为机体最丰富的溶血甘油磷脂, 在周围代谢器官和神经系统均发挥重要的生理功能. 在肥胖、糖尿病、NAFLD等代谢性疾病发生时, 血液中LPCs浓度普遍降低. 越来越多的证据表明, 多种LPCs与BMI、血糖、胰岛素敏感性等代谢指标相关, 可以作为肥胖及相关代谢性疾病的生物标记物. 此外, LPCs通过其下游受体或靶分子, 发挥改善组织代谢、缓解炎症等直接效应. 深入研究其保护性作用, 特别是对不同碳链和不同饱和度LPCs分别进行探索, 有助于为肥胖相关代谢性疾病的诊疗打开新思路.

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# Research progress of lysophosphatidylcholines in obesity-related metabolic diseases

HONG Ye, NI Yan & FU JunFen*

*Endocrinology Department, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou 310052, China*

** Corresponding author, E-mail: jjf68@zju.edu.cn*

Lysophosphatidylcholines (LPCs) are the most abundant lysophospholipids in humans. LPCs signal target proteins or are metabolized into other phospholipids that play essential physiological roles in the central nervous system and peripheral metabolic organs. Clinical studies have indicated that the concentration of circulating LPCs decreases in patients with obesity, diabetes, and nonalcoholic fatty liver diseases. A correlation was noted between LPC concentration and anthropometric measurements or blood detection indicators, which help distinguish obesity from related metabolic diseases effectively and predict disease severity as potential biomarkers. Additionally, LPCs influence the improvement of obese phenotypes, alleviation of inflammation, and inhibition of de novo lipogenesis. This review has comprehensively presented basic metabolisms and physiological roles of LPCs and explored changes in their concentrations and functions in obesity-related metabolic diseases to develop novel therapeutic and diagnostic methods.

**lysophosphatidylcholines, lipid metabolism, obesity, obesity-related metabolic diseases**

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